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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/944,163	SCHALL ET AL.	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8-13,29 and 31-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,8-13,29 and 31-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 19, 2004 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed May 19, 2004, and amendment and response, filed May 19, 2004 wherein claims 41-42 are newly submitted; the instant specification has been amended as to page 1, the first paragraph for indicating the priority for this application.

As recorded in the Advisory Action March 31, 2004, Applicant's amendment March 17, 2004 has been entered, wherein claims 5, 8, 29, and 31-40 have been amended and claims 1-4, 6-7, 14-28 and 30 are cancelled.

Currently, claims 5, 8-13, 29, 31-41 and 42 are pending in this application

Claims 5, 8-13, 29, 31-41 and 42 are examined on the merits herein.

Applicant's declarations of Brian E. McMaster (inventor) and Edward S. Mocarski (not inventor) submitted May 19, 2004 under 37 CFR 1.132, are acknowledged and will be further discussed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 41 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular compounds recited in claims 9, 29, and 41 employed in claimed method herein, does not reasonably provide enablement for any compounds encompassed by claims 5 and 41.

The instant specification fails to provide sufficient information that would allow the skilled artisan to **fully** practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method for treating CMV infection in a human.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability and the presence or absence of working examples and the quantity of experimentation necessary as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the specification, in particular, the working examples merely show that only two particular compounds octoclothepin and methiothepin were tested in vitro as US28 receptors. Note that these two particular compounds have structures when all X and Y are C or CH, and N(Het) is piperazine ring.

However, the compounds encompassed by claims 5 and 41 herein such as when X^1, X^2 X^3, X^4 are N and/or Y^1, Y^2, Y^3 Y^4 are N, or $N^{(Het)}$, can have triazine, diazine, or piperidine, or combinations thereof. These compounds do not share the central and critical common core of structure as octoclothepin and methiothepin wherein all X and Y are C or CH, not N at all (both X and Y rings are benzene rings). They are classified in different subclasses of class 514, for example, triazine 514/241, diazine 514/247, piperidine 514/315. Therefore, they are separate and patentably distinct compounds from the instant compounds recited in the claims.

Thus, octoclothepin and methiothepin tested in the working examples of the specification are **not** deemed to have same or substantial similar physical, chemical, biological and physiological properties or activities as the compounds having triazine, diazine, or piperidine, or combinations thereof. Therefore the enabling evidence for octoclothepin and methiothepin in the declaration is not considered to represent each and every compound encompassed by the claims.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds recited in the instant claims suitable to practice the claimed invention, for example, test all compounds or those having substantially similar structures encompassed by the claims, i.e., test those having triazine, diazine, or piperidine, or combinations thereof what are their therapeutic effects and toxic profiles and whether they can be used in the claimed method to be administered to a human, which must require additional or future research. Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims employed in the claimed method to be administered to a human, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 8-13, 29, 31-41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Protiva et al. (4,243,805, of record) in view of in view of the Merck Manual of Diagnosis and Therapy (17th ED, of record) and Michelson ("AT", PTO-1449 submitted May 12, 2003, of record) and Kinnear et al. Society for Neuroscience Abstracts, (1999) Vol. 25, No. 1-2, pp. 571 (Meeting Abstract).

Protiva et al. discloses that the compounds of formula (1) which are the instant preferred compounds in claims 7-13 and 30-33, and which are also known small organic compounds having a molecular weight of less than 800 daltons, have psychotropic and neurotropic activity and are useful as neuroleptics (see abstract, col.1-4 in particular).

Note that Protiva et al. discloses the effective amounts of the compound herein in the range of 10 mg to 25 mg/day (see col.27 lines 14-24), which are within or overlapping with the effective amounts 2-2000 mg/day, indicated in Applicant's specification (see page 16 lines 10-18 of the specification).

Protiva et al. does not expressly disclose the employment of the particular compounds in a method for treating CMV infection in a human or slowing the progression of CMV dissemination in the human, and wherein the chemokine is fractalkine.

The Merck Manual of Diagnosis and Therapy (17th ED) teaches that CMV infection is manifested by severe brain damage, CNS damage or CNS involvement in a human. See the right column of page 1295 to the left column of page 1296.

Michelson teaches that CMV infection can cause mental retardation in a human and CMV infects and/or replicates in a wide of variety of cell types, e.g., neurophils (see the left column of page 286).

Kinnear et al. teaches neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system (CNS). It is known that encephalitis in patients with AIDS can be caused by cytomegalovirus (CMV) (see Applicant's admissions in the "Background of Invention" of specification at page 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular compounds of formula (1) of Protiva et al. in a method for treating CMV infection in a human.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular compounds of formula (1) of Protiva et al. in a method for treating CMV infection in a human, since these particular compounds are known to have psychotropic and neurotropic activity and useful as neuroleptic agents according to Protiva et al. It is known that CMV infection is manifested by severe brain damage, CNS damage or CNS involvement in a human, according The Merck Manual of Diagnosis and Therapy, and it is also known that CMV infection can cause mental retardation in a human and CMV infects and/or replicates in a wide of variety of cell types, e.g., neurophils, according to Michelson. Neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system according to the teachings of Kinnear et al. It is known that encephalitis in patients with AIDS can be caused by cytomegalovirus (CMV) (see Applicant's admissions in the "Background of Invention" of specification at page 1).

Thus, the patient population encompassed by Protiva et al. is deemed to encompass or overlap or coincide the patient herein having CMV infection, e.g., in need of neuroprotection in the central nervous system due to brain damage or CNS damage by CMV infection, or suffering from HIV-1 encephalitis caused by CMV, or having neuronal fractalkine expression in HIV-1 encephalitis caused by CMV.

Therefore, one of ordinary skill in the art would have reasonably expected that the particular compounds of formula (1) of Protiva et al. would have beneficial therapeutic effects in treating CMV infection in a human in need of neuroprotection in the central nervous system due to brain damage or suffering from HIV-1 encephalitis

caused by CMV, or having neuronal fractalkine expression in HIV-1 encephalitis, by administering the same effective amounts of the same compound of Protiva et al. since these compounds have psychotropic and neurotropic activity and useful as neuroleptics.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 5, 8-13, 29, 31-41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sindelar et al. (of record) in view of in view of the Merck Manual of Diagnosis and Therapy (17th ED) (PTO-892) and Michelson ("AT", PTO-1449 submitted May 12, 2003) and Kinnear et al. Society for Neuroscience Abstracts, (1999) Vol. 25, No. 1-2, pp. 571 (Meeting Abstract).

Sindelar et al. discloses that the compounds of formula (I), octoclothepin and methiothepin in particular which are the instant preferred compounds in claims 30-34, and which are also known small organic compounds having a molecular weight of less than 800 daltons, have psychotropic and neurotropic activity and are useful as neuroleptics (see title and abstract).

Sindelar et al. does not expressly disclose the employment of the particular compounds in a method for treating CMV infection in a human, and wherein the chemokine is fractalkine.

The Merck Manual of Diagnosis and Therapy (17th ED) teaches that CMV infection is manifested by severe brain damage, CNS damage or CNS involvement in a human. See the right column of page 1295 to the left column of page 1296.

Michelson teaches that CMV infection can cause mental retardation in a human and CMV infects and/or replicates in a wide of variety of cell types, e.g., neurophils (see the left column of page 286).

Kinnear et al. teaches neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system (CNS). It is known that encephalitis in patients with AIDS can be caused by cytomegalovirus (CMV) (see Applicant's admissions in the "Background of Invention" of specification at page 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular compounds of formula (1) of Sindelar et al. in a method for treating CMV infection in a human.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular compounds of formula (1) of Sindelar et al. in a method for treating CMV infection in a human, since these particular compounds are known to have psychotropic and neurotropic activity and useful as neuroleptics according to Protiva et al. It is known that CMV infection is manifested by severe brain damage, CNS damage or CNS involvement in a human, according The Merck Manual of Diagnosis and Therapy, and it is also known that CMV infection can cause mental retardation in a human and CMV infects and/or replicates in a wide of variety of cell types, e.g., neurophils, according to Michelson. Neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system according to the teachings of Kinnear et al. It is known that encephalitis

in patients with AIDS can be caused by cytomegalovirus (CMV) (see Applicant's admissions in the "Background of Invention" of specification at page 1).

Thus, the patient population encompassed by Sindelar et al. is deemed to encompass or overlap or coincide the patient herein having CMV infection, e.g., in need of neuroprotection in the central nervous system due to brain damage or CNS damage by CMV infection, or suffering from HIV-1 encephalitis caused by CMV, or having neuronal fractalkine expression in HIV-1 encephalitis caused by CMV.

Therefore, one of ordinary skill in the art would have reasonably expected that the particular compounds of formula (1) of Sindelar et al. would have beneficial therapeutic effects in treating CMV infection in a human in need of neuroprotection in the central nervous system due to brain damage or suffering from HIV-1 encephalitis caused by CMV, or having neuronal fractalkine expression in HIV-1 encephalitis, since these compounds have psychotropic and neurotropic activity and useful as neuroleptics.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments and declarations under 37 CFR 1.132 of Brian E. McMaster and Edward S. Mocarski and Appendix submitted May 19, 2004 with respect to the rejections made under 35 U.S.C. 103(a) of record in the previous Office Action January 14, 2004 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

First, Applicant's arguments regarding the inherency under 35 U.S.C. 102(b) are moot since the instant claims are rejected under 35 U.S.C. 103(a) in the prior Office Action mailed January 14, 2004, and no anticipation rejection is currently applied.

Secondly, Applicant's arguments with respect to the rejections made under 35 U.S.C. 103(a) of record are believed to be adequately addressed by the obvious rejection presented above.

Further, the declaration of Brian E. McMaster and Edward S. Mocarski under 37 CFR 1.132 has been fully considered but are not deemed persuasive since the declaration primarily discusses the mechanism of action of the treatment proposed by Applicant, i.e., binding the CMV U28 receptor. Note that the mechanism of action of a treatment does not have a bearing on the patentability of the invention if the method steps are already known. Applicant's recitation of a new mechanism of action for the prior art method will not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps.

Additionally, the declarations herein are ineffective to overcome the previous 103(a) rejection herein since the declarations merely present statements or opinions regarding the proposed mechanism of action herein and citing inconclusive studies of others (see Appendix provided by Applicant), but fails to set forth any factual evidences. Therefore, the declarations are insufficient to rebut the prima facie case herein.

As pointed out in the Advisory Action, Applicants aver surprising or unexpected results residing in the claimed subject matter. However, Applicant's Examples 1-3 of the specification at pages 17-18 herein have been fully considered but are not deemed

persuasive as to the nonobviousness and/or unexpected results of the claimed invention over the prior art, since the testing in *vitro* in Examples 1-3 provides no clear and convincing evidence for treating CMV infection in a human. Evidence as to unexpected benefits must be" clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963). Applicant has the burden to explain the experimental evidence. See *In re Borkowski and Van Venrooy* 184 USPQ 29 (CCPA 1974).

Note that it is well-settled that the evidence including a comparison with the closest prior art is one of elements to be considered as unexpected results (see for example, *In re Merchant*, 575 F.2d 865, 869, 197 USPQ 785, 788 (CCPA 1978), which is provided either in the specification or an affidavit or declaration submitted during prosecution on the issue.

Again, arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135,139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a).

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
August 5, 2004